Psychiatric Research Applied to Clinical Practice

Augmentation and Combination Strategies to Treat the Residual Symptoms of Major Depressive Disorder

by Maurizio Fava, MD; and Steven D. Targum, MD

This month's installment features an interview with Maurizio Fava, MD, Vice-Chair, Department of Psychiatry, Massachusetts General Hospital and Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts.

Experienced clinicians are increasingly aware of the limitations of antidepressant monotherapies to completely treat the acute symptoms of major depressive disorder (MDD) and to sustain the benefits over time. In fact, many patients with MDD who are treated with SSRIs achieve only partial treatment responses and may suffer from residual symptoms contributing to a poorer outcome.[1] Consequently, the "old school" teaching of reluctant polypharmacy is being recast as a more strategic new approach incorporating augmentation or combination antidepressant treatments. In this interview, Dr. Maurizio Fava reviews the importance of treating residual symptoms and describes some of his preferred strategies.

DO RESIDUAL SYMPTOMS MATTER?

Dr. Fava: They matter a lot. Partial treatment responders may suffer from persistent psychological, behavioral, and somatic symptoms, including sadness, anhedonia, guilt, fatigue, insomnia, decreased appetite, decreased motivation, cognitive deficits, and even pain.[1] Furthermore, these patients are highly susceptible to relapse. Depressed patients with residual symptoms have poorer prognoses and tend to function worse over time. In one study of long-term outcome, 76 percent of treated patients with persistent, residual symptoms relapsed within 10 months, in contrast to only 25 percent of patients without residual symptoms.[2] So, in my opinion, achieving full symptom remission is the ultimate objective in the treatment of depressed patients.

HOW DO YOU DEFINE SYMPTOM REMISSION?

Dr. Fava: One way to determine a remission status is to use a rating instrument, such as the Hamilton rating scale for depression. Using the 17-item version of this scale, total scores <8 have been traditionally used to define symptom remission. This means that some residual symptoms may remain, but most of these patients are much improved and able to function.

USING THAT STANDARD, HOW MANY DEPRESSED PATIENTS ACTUALLY ACHIEVE SYMPTOM REMISSION?

Dr. Fava: On adequate monotherapy, only a minority of depressed patients achieve symptom remission. In fact, meta-analyses of well conducted, double-blind, antidepressant trials of nonchronic patients with MDD revealed remission rates between 30 and 45 percent on monotherapy alone.[3,4] The recent NIMH-funded STAR-D study[4] confirmed this finding: In general, only one in three patients in the first sequence of monotherapy treatment achieved symptomatic remission.

ARE THERE THERAPEUTIC STRATEGIES THAT CAN INCREASE THE RATE OF SYMPTOMATIC REMISSION?

Dr. Fava: Yes…and some are quite obvious. Clearly, encouraging treatment adherence at adequate doses for an adequate duration (at least 6–12 weeks) will help. It has also been shown that both psychoeducation and cognitive therapy can enhance symptomatic remission and sustain clinical benefits as well. Beyond that, many clinicians are using augmentation or combination pharmacotherapy to increase the rate of remission.[3,5,6]

WHAT IS THE DIFFERENCE BETWEEN AUGMENTATION AND COMBINATION TREATMENTS?

Dr. Fava: Augmentation treatment involves the addition of a medication that is not considered a standard antidepressant drug, like thyroid supplementation to a typically used antidepressant. Alternatively, combination treatments involve the use of two known antidepressants simultaneously.

WHAT ARE SOME EXAMPLES OF AUGMENTATION STRATEGIES FOR CLINICAL PRACTICE?

Dr. Fava: First, it's important to emphasize that all of these approaches are off-label strategies because they have not been approved by the FDA.

Despite the lack of approval, some augmentation strategies have been around for a long time. For instance, tricyclic antidepressants (TCAs) were combined with conventional antipsychotics in the 1970s (amitryptiline and perphenazine) to treat anxious-depressed patients prior to concerns about tardive dyskinesia. Lithium (600mg daily) was frequently used as an augmenter to TCAs in the 1980s. However, lithium is not particularly effective when added to SSRIs or SNRIs, and three recent double-blind studies of lithium augmentation actually failed. On the other hand, l-triiodothyronine (T3) augmentation was somewhat, although not significantly better than lithium in Level 3 of STAR*D.[5]

Other augmentation strategies have included buspirone (5-HT-1a receptor partial agonist), pindolol (a beta blocker), dopaminergic drugs, modafinil, anticonvulsants, hormones (estrogen, testosterone), and psychostimulants.[1]

A recent double-blind, placebo-controlled modafinil study was particularly interesting: Patients with residual fatigue and excessive sleepiness on SSRIs improved significantly when modafinil was added to SSRI monotherapy.[1]

Lately, I've been interested in the one-carbon cycle compounds like folate, methylfolate, or s-adenosylmethionine (SAMe) to enhance remission rates and help nonresponders. We are currently conducting the first double-blind, placebo-controlled studies of SAMe and l-methylfolate.

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LET'S DISCUSS COMBINATION STRATEGIES. HOW DO THEY DIFFER FROM OLD SCHOOL POLYPHARMACY?

Dr. Fava: It's no longer simply an add-on approach. We focus on combining known antidepressants with different mechanisms of action. In addition, combination strategies may allow us to use lower doses of each drug and thereby minimize the side effect profile.

There are very few double-blind studies of combination strategies, and most have employed full doses of both drugs in which one was added when the first treatment did not yield symptomatic remission. Some combinations have included

bupropion, reboxetine, or mirtazapine with SSRIs, as well as TCAs with SSRIs.[7,8] Although widely used, the combination of bupropion with SSRIs is only partially supported by the results of Level 2 of STAR*D.[3] In a group of 565 patients who had not responded to 12 weeks of citalopram therapy, both sustained release bupropion and buspirone augmentation achieved remission in about 30 percent of patients.[3] Augmentaion with bupropion was better tolerated than buspirone in that study. We definitely need more data, but I am optimistic that combinations will offer enhanced remission in many patients.

the increments we had hoped over the first treatment intervention.[4] This novel combined approach from the outset is clearly more aggressive and different from the traditional sequential approach, but given the disappointing results from monotherapy it may be worth considering in some MDD patients.

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DR. FAVA, WHAT'S YOUR BEST STRATEGY FOR IMPROVING REMISSION RATES?

Dr. Fava: In my opinion, the best new strategy is not to wait at all to combine drugs. Generally, augmentation or combination strategies are considered only when the initial monotherapy treatment has failed to achieve remission after 3 to 6 weeks or longer. The use of these strategies at the initiation of treatment could potentially improve adherence as well as provide earlier treatment response by broadening the spectrum of action. The STAR-D results clearly demonstrate that the second-, third-, and fourth-sequenced treatments do not offer

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